PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

The Accompanying Application

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Entry into National Phase of International Application No.: PCT/GB01/02572 under 35 U.S.C. § 371

For : SERINE PROTEASE INHIBITORS

Docket No. : 00218US

PRELIMINARY AMENDMENT ON FILING

Attention: DO/EO

Box PCT

Assistant Commissioner for Patents

Washington, DC 20231

Sir:

Before calculating the filing fee, please amend the accompanying application as follows:

Please add the Abstract attached on a separate sheet.

In the Description

At page 91, line 11 to page 92, line 2, please delete the paragraphs corresponding to Examples 14, 14a and 15.

At page 100, line 9, immediately above "Assay Protocols", please add the following compounds to the list of compounds:-

1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[(R)-(3-hydroxy-methylpyrrolidin-1-yl)methyl]piperidine Trifluoroacetate Salt

1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[(R)-(3-hydroxy-methylpyrrolidin-1-yl)methyl]piperidine Hydrochloride Salt

1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[(S)-(3-hydroxy-methylpyrrolidin-1-yl)methyl]piperidine Trifluoroacetate Salt

In the Claims

Please cancel Claims 14, 15, 22, 23, 25 and 26 (without prejudice); enter the indicated amendments to Claims 3 to 8, 10 to 13, 16 to 21; and enter new Claims 27-31. Directions for amendment of claims are indicated on the copy of the attached hand amended ("marked up") original claims, showing in manuscript the amendments that have been made and the origins of the new claims. Clean forms of new and rewritten claims are included in the attached "Clean Pending Claims" document.

Remarks

This application seeks protection for certain novel compounds that are inhibitors of the serine protease, Factor Xa, and are useful for the treatment of thrombotic disorders. It is the national stage of an international

application, the claims of which were drafted in accordance with international practice.

Applicants now wish to amend the application to bring it into conformity with United States patent practice.

For the assistance of the Examiner, a copy of the original claims is attached, as noted above, showing in manuscript the amendments that have been made.

Claims 14, 15, 22, 23, 25 and 26 have been canceled, without prejudice.

Claims 3 to 8, 10, 12, 13 and 16 to 21 have been rewritten in single dependent form.

Claim 11 has been rewritten in multiple dependent form. Claim 20 now depends from this claim.

New claim 27 is based upon a combination of original claims 1, 8, 10, 20, 18 and 3. It is noted that all of the original claims were drafted in multiple dependent form, and hence new claim 27 is fully based on these original claims.

New claim 28 is based upon new claim 27, and additionally incorporates the subject matter of Claim 5.

New claim 29 is based upon new claim 28, and additionally incorporates the subject matter of Claim 9.

New claim 30 is based upon new claim 29, and additionally incorporates the subject matter of Claim 19.

New claim 31 is based upon new claim 30, and page 15, line 12 (where phenyl is noted to be a value of particular interest for Cy).

Error in the Description

Applicants have discovered an error in each of Examples 14, 14a and 15. The compounds actually prepared and tested contained a 2-hydroxymethylpyrrolidin-1-yl group, not a 3-hydroxymethylpyrrolidin-1-yl group.

In view of the statement at page 103, lines 25 to 27 of the description to the effect that the exemplified compounds have been tested in Assay 1 or Assay 2, Applicants consider that it would be most appropriate to delete Examples 14, 14a and 15. However, Applicants believe that the compounds of Examples 14 and 15 would be active if made and tested, and accordingly propose to retain their names in the list of compounds following Example 28. It is respectfully submitted that no new matter has been introduced into the specification by retaining their names to the list, because each of the three named compounds was disclosed in the international application as originally filed.

Favorable consideration of the application is requested.

Respectfully submitted,

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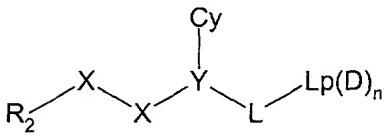
UNITED KINGDOM

February 1, 2002

Attachments: Abstract on separate sheet
Hand-amended (marked-up) Claims
Clean Pending Claims

Clean Set of Claims

1. A serine protease inhibitor compound of formula (I)



(I)

wherein:

R_2 is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_{1a} independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R_1 is as defined for R_{1a}, provided that R_1 is not unsubstituted aminoalkyl;

Y (the α-atom) is a nitrogen atom or a CR_{1b} group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups R_{3a} or phenyl optionally substituted by R_{3a} or $R_{3i}X_i$;

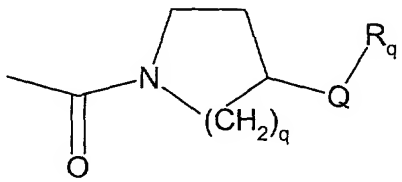
each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkyloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S; and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or $-OCH_2O-$ which is bonded to two adjacent ring atoms in Cy;

X_i is a bond, O, NH or CH_2;

R_{3i} is phenyl, pyridyl or pyrimidinyl optionally substituted by R_{3a};

R_{1b}, R_{1c} and R_{1j} are as defined for R_{1a}; and

$-L-Lp(D)_n$ is

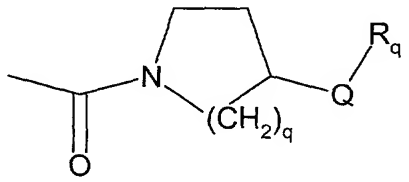


q is 1 or 2;

Q is methylene; and R_q is NR_aR_b in which each of R_a and R_b independently is hydrogen or C_{1-3}alkyl; or one of R_a and R_b is hydrogen or methyl and the other of R_a and R_b is (3-6C)cycloalkyl, pyrid-4-yl, $-CH_2-R_c$ or $-CH_2-R_d$ in which R_c is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, $CONH_2$, SO_2NH_2, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and in which R_d is isopropyl or

cyclopentyl, or NR_aR_b is azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, or tetrahydro-1,4-diazepino [in which a pyrrolidino or piperidino may be a 3,4-didehydro derivative and in which a azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, or tetrahydro-1,4-diazepino may be optionally substituted on a ring carbon atom by hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl (provided that the amino, hydroxy or alkoxy substituent is not on a ring carbon atom which is included in a double bond, or adjacent to a ring oxygen, sulfur or nitrogen atom) and in which the piperazino or tetrahydro-1,4-diazepino may bear a methyl group at the 4-position];
or a physiologically-tolerable salt thereof.

2. A compound according to claim 1 wherein $-L-Lp(D)_n$ is of the formula:



wherein:
q is 1 or 2;
Q is methylene; and R_q is NR_aR_b in which each of R_a and R_b independently is hydrogen or C_{1-3}alkyl; or one of R_a and R_b is hydrogen or methyl and the other of R_a and R_b is $-CH_2-R_c$ or $-CH_2-R_d$ in which R_c is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, $CONH_2$, SO_2NH_2, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and in which R_d is isopropyl or cyclopentyl, or NR_aR_b is pyrrolidino, piperidino, morpholino, piperazino, or tetrahydro-1,4-diazepino in which a pyrrolidino or piperidino

may be a 3,4-didehydro derivative and in which a pyrrolidino, piperidino, piperazino, or tetrahydro-1,4-diazepino may bear a methyl group at the 4-position;
or a physiologically-tolerable salt thereof.

3. (amended) A compound according to claim 1 wherein q is 2.

4. (amended) A compound according to claim 1 wherein R_q is NR_aR_b in which R_a is hydrogen or C_{1-3}alkyl and R_b is C_{1-3}alkyl; or R_a is hydrogen and R_b is (3-6C)cycloalkyl or pyrid-4-yl; or NR_aR_b is azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino or piperazino [in which a pyrrolidino, piperidino or piperazino may be optionally substituted on a ring carbon atom by hydroxy or hydroxymethyl (provided that the hydroxy substituent is not on a ring carbon atom which is adjacent to a ring nitrogen atom) and in which the piperazino may bear a methyl group at the 4-position].

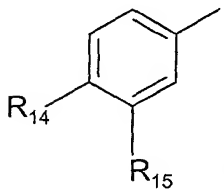
5. (amended) A compound according to claim 1 wherein Rq is selected from dimethylamino, diethylamino, prop-2-ylamino, pyrrolidino, 3-pyrrolino, 3-hydroxypyrrolidino, 3-hydroxymethylpyrrolidino, piperidino, 3-hydroxypiperidino, 4-hydroxypiperidino, 4-hydroxymethylpiperidino, piperazino and 4-methylpiperazino.

6. (amended) A compound according to claim 1 wherein R_2 is phenyl, thien-2-yl, naphthyl, indol-2-yl, indol-6-yl, benzo[b]furan-5-yl, benzo[b]thiophen-2-yl or benzimidazol-2-yl (each of which is optionally substituted as defined in claim 1).

7. (amended) A compound according to claim 6 wherein optional substituents for R_2 are selected from:
fluoro, chloro, bromo, iodo, nitro, thiol, difluoromethoxy,

trifluoromethoxy, hydrazido, methylhydrazido, amino, cyano, trifluoromethyl, methylthio, vinyl, ethynyl, acetylamino, carboxy, acetoxy, hydroxy, methyl, ethyl, amido ($CONH_2$), aminomethyl, methoxy and ethoxy.

8. (amended) A compound according to claim 1 wherein R_2 is selected from one of the formula (A') to (H'):



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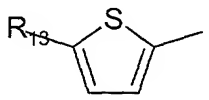

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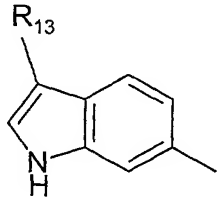

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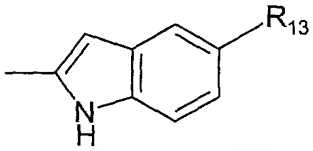

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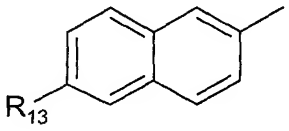

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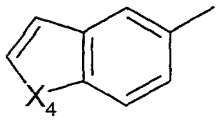

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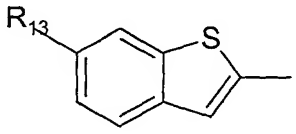

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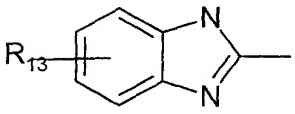


(H')

wherein X_4 is O or S, R_{13} is selected from hydrogen, chloro or methyl and R_{14} is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and R_{15} is selected from hydrogen, methyl, fluoro, chloro and amino.

9. A compound according to claim 8, wherein R_2 is 4-

methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl.

10. (amended) A compound according to claim 1 wherein -X-X- is -CONH-.

11. (amended) A compound according to any one of claims 1 to 10, 12 to 13 and 16 to 19, wherein Y is CH.

12. (amended) A compound according to claim 1 wherein Cy is an optionally R_{3a} substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl, furanyl, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, imidazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrimidinyl, pyridazinyl, quinoloyl, isoquinolyl, benzofuryl, benzothienyl or cycloalkyl group, or a phenyl group substituted by $R_{3i}X_i$ in which X_i is a bond, O, NH or CH_2 and R_{3i} is phenyl optionally substituted by R_{3a}.

13. (amended) A compound according to claim 1 wherein Cy is an optionally R_{3a} substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl or cycloalkyl group.

14. (cancelled on national phase entry).

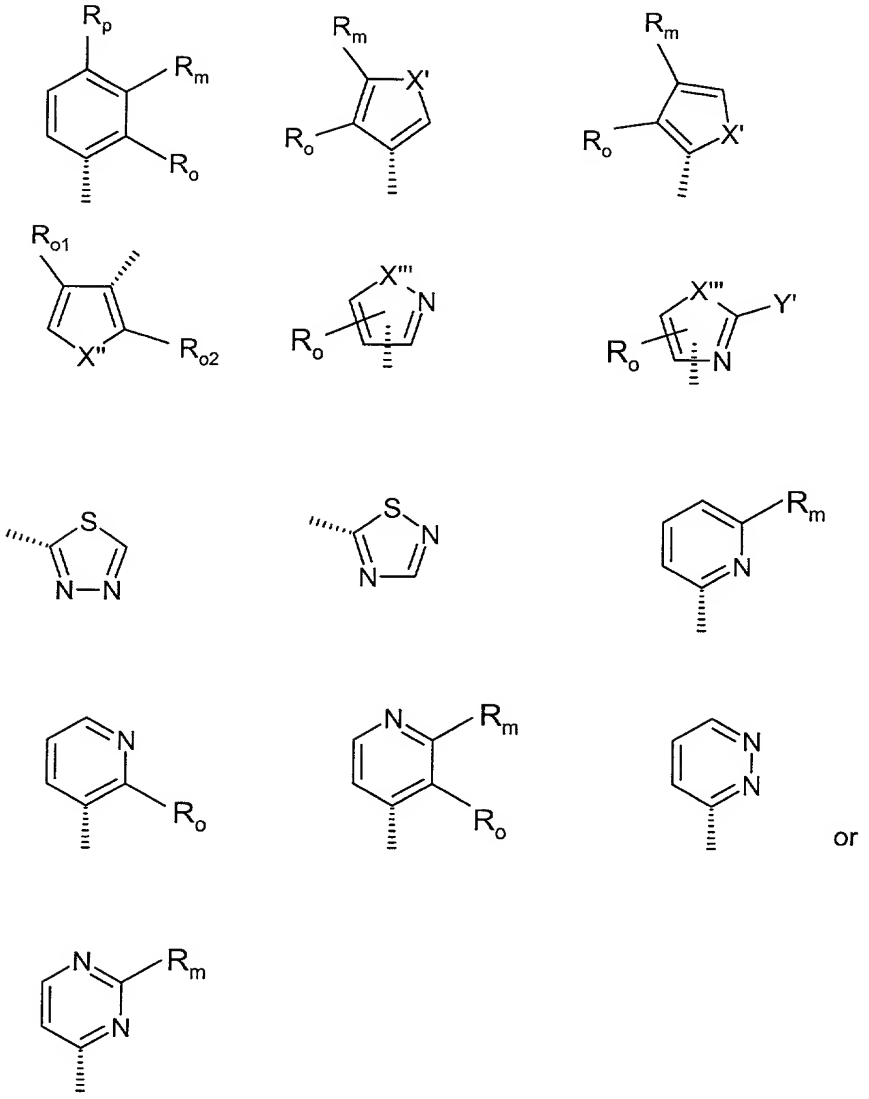
15. (cancelled on national phase entry).

16. (amended) A compound according to claim 12 wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro,

chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl or morpholin-1-ylcarbonyl and $-OCH_2O-$ (which is bonded to two adjacent ring atoms in Cy).

17. (amended) A compound according to claim 13 wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and trifluoromethyl.

18. (amended) A compound according to claim 1 wherein Cy is selected from:



or

wherein:

X' is selected from O, S and NMe;

X'' is selected from O and S;

X''' is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;

R_o is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and methylsulphonyl;

R_m is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the

formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S, and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);
R_p is selected from hydrogen and fluoro; or
R_o and R_m or R_m and R_p form an $-OCH_2O-$ group; or
R_o and R_m together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroary ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur); and
one of R_{o1} and R_{o2} is hydrogen and the other is R_o.

19. (amended) A compound according to claim 18 wherein Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-yl, naphth-1-yl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl and quinolin-8-yl.

20. (amended) A compound as claimed in Claim 11, in which the alpha atom in Y is carbon and has the conformation that would result from construction from a D-α-aminoacid $NH_2-CR_{1b}(Cy)-COOH$ where the NH_2 represents part of X-X.

21. (amended) A pharmaceutical composition, which comprises a compound as claimed in claim 1 together with at least one pharmaceutically acceptable carrier or excipient.

22. (cancelled on national phase entry).

23. (cancelled on national phase entry).

24. A method of treatment of a human or non-human animal body

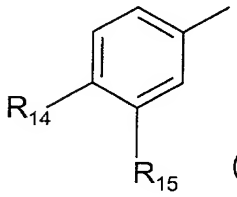
to combat a thrombotic disorder, which comprises administering to said body an effective amount of a compound as claimed in claim 1.

25. (cancelled on national phase entry).

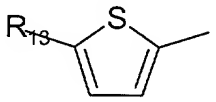
26. (cancelled on national phase entry).

27. (new) A compound according to claim 1 wherein:-

R_2 is selected from one of the formula (A') to (H'):



(A')



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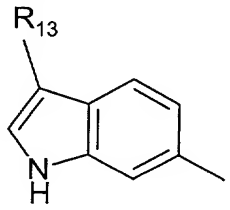

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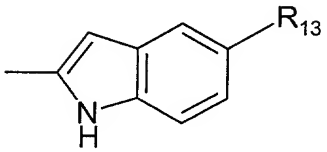

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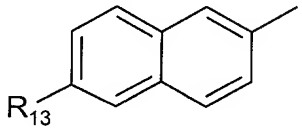

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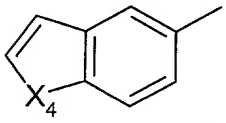

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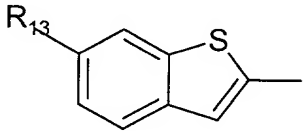

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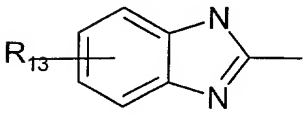


(H')

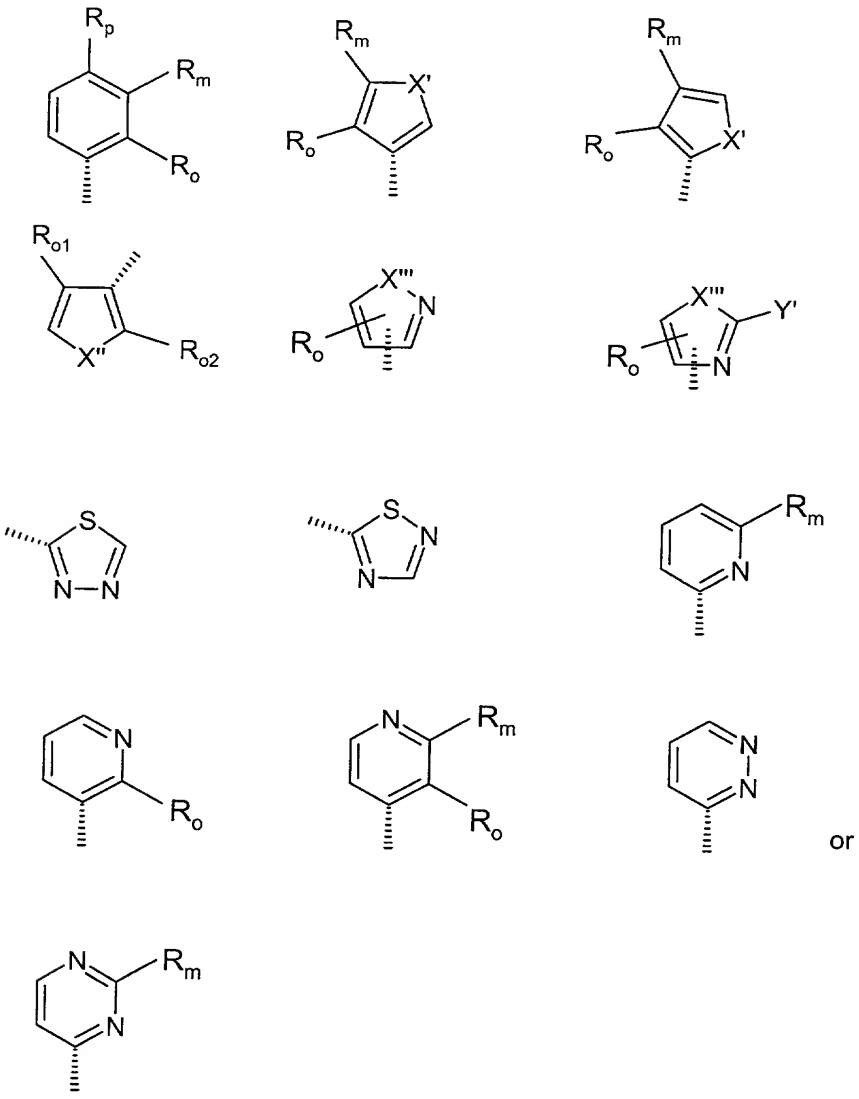
wherein X_4 is O or S, R_{13} is selected from hydrogen, chloro or methyl and R_{14} is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and R_{15} is selected from hydrogen,

methyl, fluoro, chloro and amino;

-X-X- is -CONH-;

Y is CH and has the conformation that would result from construction from a D-α-aminoacid NH_2-CR_{1b}(Cy)-COOH where the NH_2 represents part of X-X;

Cy is selected from



or

wherein:

X' is selected from O, S and NMe;

X'' is selected from O and S;

X''' is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;
R_o is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and methylsulphonyl;
R_m is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S, and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);
R_p is selected from hydrogen and fluoro; or
R_o and R_m or R_m and R_p form an $-OCH_2O-$ group; or
R_o and R_m together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroary ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur); and
one of R_{o1} and R_{o2} is hydrogen and the other is R_o; and
q is 2.

28. (New) A compound according to claim 27 wherein Rq is selected from dimethylamino, diethylamino, prop-2-ylamino, pyrrolidino, 3-pyrrolino, 3-hydroxypyrrolidino, 3-hydroxymethylpyrrolidino, piperidino, 3-hydroxypiperidino, 4-hydroxypiperidino, 4-hydroxymethylpiperidino, piperazino and 4-methylpiperazino.

29. (New) A compound according to Claim 28 wherein R_2 is 4-methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl.

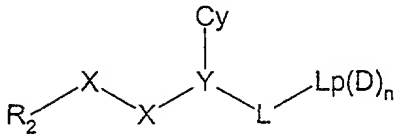
30. (New) A compound according to claim 29 wherein Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-4-yl, thien-2-yl, thien-

3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-yl, naphth-1-yl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl and quinolin-8-yl.

31. (New) A compound according to claim 30 wherein Cy is phenyl.

Claims

1. A serine protease inhibitor compound of formula (I)



(I)

wherein:

R_2 is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_{1a} independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R_1 is as defined for R_{1a}, provided that R_1 is not unsubstituted aminoalkyl;

Y (the α-atom) is a nitrogen atom or a CR_{1b} group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups R_{3a} or phenyl optionally substituted by R_{3a} or $R_{3i}X_i$;

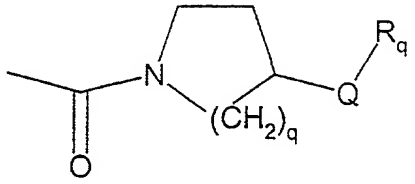
each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkyloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S; and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or $-OCH_2O-$ which is bonded to two adjacent ring atoms in Cy;

X_i is a bond, O, NH or CH_2;

R_{3i} is phenyl, pyridyl or pyrimidinyl optionally substituted by R_{3a};

R_{1b}, R_{1c} and R_{1j} are as defined for R_{1a}; and

$-L-Lp(D)_n$ is



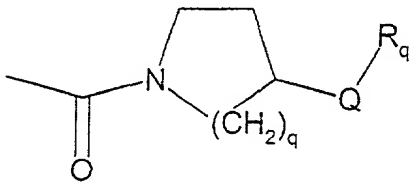
q is 1 or 2;

Q is methylene; and R_q is NR_aR_b in which each of R_a and R_b independently is hydrogen or C_{1-3}alkyl; or one of R_a and R_b is hydrogen or methyl and the other of R_a and R_b is (3-6C)cycloalkyl, pyrid-4-yl, $-CH_2-R_c$ or $-CH_2-R_d$ in which R_c is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, $CONH_2$, SO_2NH_2, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and in which R_d is isopropyl or

cyclopentyl, or NR_aR_b is azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, or tetrahydro-1,4-diazepino [in which a pyrrolidino or piperidino may be a 3,4-didehydro derivative and in which a azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, or tetrahydro-1,4-diazepino may be optionally substituted on a ring carbon atom by hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl (provided that the amino, hydroxy or alkoxy substituent is not on a ring carbon atom which is included in a double bond, or adjacent to a ring oxygen, sulfur or nitrogen atom) and in which the piperazino or tetrahydro-1,4-diazepino may bear a methyl group at the 4-position];

or a physiologically-tolerable salt thereof.

2. A compound according to claim 1 wherein $-L-Lp(D)_n$ is of the formula:



wherein:

q is 1 or 2;

Q is methylene; and R_q is NR_aR_b in which each of R_a and R_b independently is hydrogen or C_{1-3}alkyl; or one of R_a and R_b is hydrogen or methyl and the other of R_a and R_b is $-CH_2-R_c$ or $-CH_2-R_d$ in which R_c is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, $CONH_2$, SO_2NH_2, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and in which R_d is isopropyl or cyclopentyl, or NR_aR_b is pyrrolidino, piperidino, morpholino, piperazino, or tetrahydro-1,4-diazepino in which a pyrrolidino or piperidino

may be a 3,4-didehydro derivative and in which a pyrrolidino, piperidino, piperazino, or tetrahydro-1,4-diazepino may bear a methyl group at the 4-position;
or a physiologically-tolerable salt thereof.

(amended)

3. A compound according to claim 1 ~~or claim 2~~ wherein q is 2.

(amended)

4. A compound according to ~~any of~~ claims 1 ~~to 3~~ wherein R_q is NR_aR_b in which R_a is hydrogen or C_{1-3}alkyl and R_b is C_{1-3}alkyl; or R_a is hydrogen and R_b is (3-6C)cycloalkyl or pyrid-4-yl; or NR_aR_b is azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino or piperazino [in which a pyrrolidino, piperidino or piperazino may be optionally substituted on a ring carbon atom by hydroxy or hydroxymethyl (provided that the hydroxy substituent is not on a ring carbon atom which is adjacent to a ring nitrogen atom) and in which the piperazino may bear a methyl group at the 4-position].

(amended)

5. A compound according to ~~any of~~ claims 1 ~~to 4~~ wherein Rq is selected from dimethylamino, diethylamino, prop-2-ylamino, pyrrolidino, 3-pyrrolino, 3-hydroxypyrrolidino, 3-hydroxymethylpyrrolidino, piperidino, 3-hydroxypiperidino, 4-hydroxypiperidino, 4-hydroxymethylpiperidino, piperazino and 4-methylpiperazino.

(amended)

6. A compound according to ~~any one of~~ claims 1 ~~to 5~~ wherein R_2 is phenyl, thien-2-yl, naphthyl, indol-2-yl, indol-6-yl, benzo[b]furan-5-yl, benzo[b]thiophen-2-yl or benzimidazol-2-yl (each of which is optionally substituted as defined in claim 1).

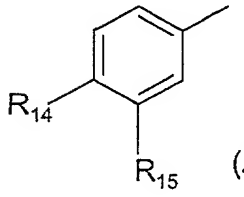
(amended)

7. A compound according to ~~any one of~~ claims ~~1 to~~ 6 wherein optional substituents for R_2 are selected from:

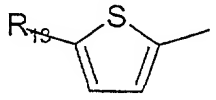
fluoro, chloro, bromo, iodo, nitro, thiol, difluoromethoxy, trifluoromethoxy, hydrazido, methylhydrazido, amino, cyano, trifluoromethyl, methylthio, vinyl, ethynyl, acetylamino, carboxy, acetoxy, hydroxy, methyl, ethyl, amido ($CONH_2$), aminomethyl, methoxy and ethoxy.

(amended)

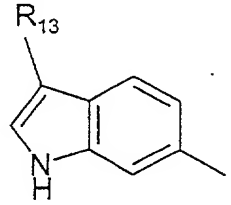
8. A compound according to ~~any one of~~ claims 1 ~~to 5~~ wherein R_2 is selected from one of the formula (A') to (H'):



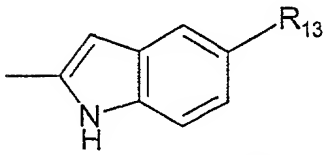
(A')



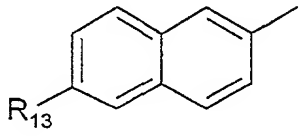
(B')



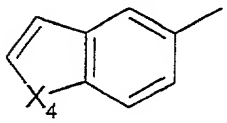
(C')



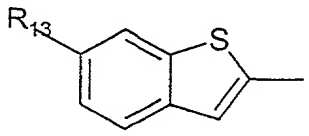
(D')



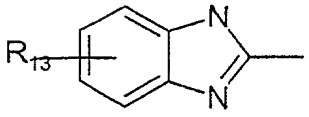
(E')



(F')



(G')



(H')

wherein X_4 is O or S, R_{13} is selected from hydrogen, chloro or methyl and R_{14} is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and R_{15} is selected from hydrogen, methyl, fluoro, chloro and amino.

9. A compound according to claim 8, wherein R_2 is 4-methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl.

(amended)

10. A compound according to ~~any one of~~ claims 1 ~~to 9~~ wherein -X-X- is -CONH-.

(amended) 16 to 19,

11. A compound according to any one of claims 1 to 10, 12 to 13 and wherein Y is CH.

(amended)

12. A compound according to ~~any one of~~ claims 1 ~~to 11~~ wherein Cy is an optionally R_{3a} substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl, furanyl, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, imidazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrimidinyl, pyridazinyl, quinoloyl, isoquinolyl, benzofuryl, benzothienyl or cycloalkyl group, or a phenyl group substituted by $R_{3i}X_i$ in which X_i is a bond, O, NH or CH_2 and R_{3i} is phenyl optionally substituted by R_{3a}.

(amended)

13. A compound according to ~~any one of~~ claims 1 ~~to 12~~ wherein Cy is an optionally R_{3a} substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl or cycloalkyl group.

(cancelled on national phase entry)

14. ~~A compound according to any one of claims 1 to 13~~ wherein R_{3a} is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), ~~alkoxycarbonylamino, amino, halo, cyano, nitro, thiol~~

~~alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido,~~ alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S; and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group) and $-OCH_2O-$ which is bonded to two adjacent ring atoms ~~in Cy1~~

(cancelled on national phase entry)

15. ~~A compound according to any one of claims 1 to 13 wherein~~ R_{3a} is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxycarbonylamino, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, ~~alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl~~

(amended)

16. A compound according to ~~any one of~~ claims ~~1 to 15~~ 12 wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl, pyrrolidin-1-ylcarbonyl,

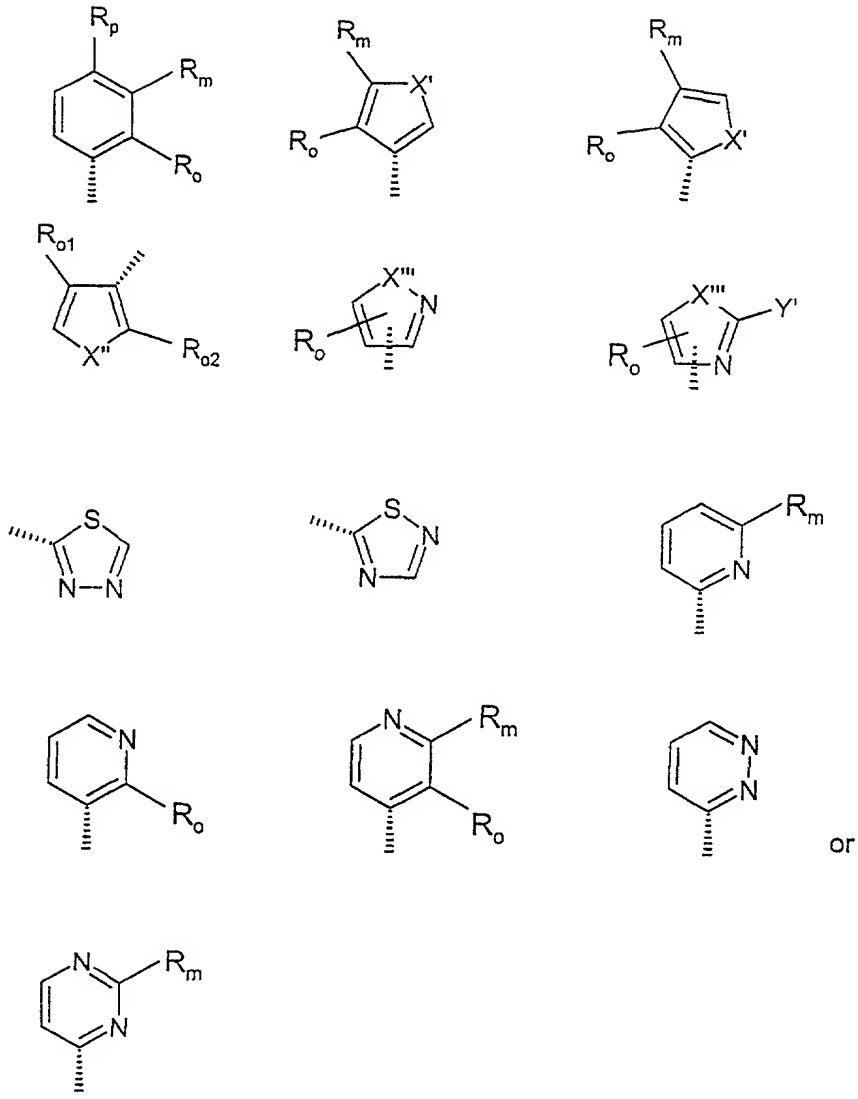
piperidin-1-ylcarbonyl or morpholin-1-ylcarbonyl and $-OCH_2O-$ (which is bonded to two adjacent ring atoms in Cy).

(amended) 13

17. A compound according to ~~any one of~~ claims ~~1 to 16~~ wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and trifluoromethyl.

(amended)

18. A compound according to ~~any one of~~ claims 1 ~~to 11~~ wherein Cy is selected from:



or

wherein:

X' is selected from O, S and NMe;

X'' is selected from O and S;

X''' is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;

R_o is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and methylsulphonyl;

R_m is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the

formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S, and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);

R_p is selected from hydrogen and fluoro; or

R_o and R_m or R_m and R_p form an $-OCH_2O-$ group; or

R_o and R_m together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroary ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur); and

one of R_{o1} and R_{o2} is hydrogen and the other is R_o.

(amended)

19. A compound according to ~~any one of~~ claims 1 ~~to 18~~ wherein Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-yl, naphth-1-yl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl and quinolin-8-yl.

(amended)

20. A compound as claimed in ~~any one of~~ Claims ~~1 to 19~~, in which the alpha atom in Y is carbon and has the conformation that would result from construction from a D-α-aminoacid $NH_2-CR_{1b}(Cy)-COOH$ where the NH_2 represents part of X-X.

(amended)

21. A pharmaceutical composition, which comprises a compound as claimed in ~~any one of~~ claims ~~1 to 20~~ together with at least one pharmaceutically acceptable carrier or excipient.

(Cancelled on national phase entry)

22. ~~A compound as claimed in any one of claims 1 to 20 for use in therapy.~~

(Cancelled on national phase entry)

23. ~~Use of a compound as claimed in any one of claims 1 to 20~~

~~for the manufacture of a medicament for the treatment of a thrombotic disorder.~~

24. A method of treatment of a human or non-human animal body to combat a thrombotic disorder, which comprises administering to said body an effective amount of a compound as claimed in claim 1.

(Cancelled on national phase entry)

25. ~~A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 20 for use to combat a thrombotic disorder.~~

(Cancelled on national phase entry)

26. ~~A compound of formula I as claimed in claim 1 and named in any of the Examples herein, or a physiologically tolerable salt thereof~~.

Add new claim 27 to 31